

International Conference on Environmental Cadmium: An Overview

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The International Conference on Environmental Cadmium was held June 7-9, 1978 on the NIH Campus in Bethesda, Maryland, to summarize the current level of scientific knowledge about cadmium as an environmental agent and to identify needed areas of research. The meeting was sponsored by the National Institute of Environmental Health Sciences and the Department of Environmental Hygiene, Karolinska Institute, as Cooperating World Health Organization Centers in collaboration with the Scientific Committee on the Toxicology of Metals under the Permanent Commission and International Association on Occupational Health. The following overview was assembled with the assistance of Dr. Gunnar Nordberg, Secretary of the Scientific Committee on the Toxicology of Metals, and persons attending the conference, but final responsibility for the summary content and attached recommendations should be regarded as that of only the conference chairman. The meeting was divided into consecutive sessions dealing with methods and problems of analysis, sources of environmental pollution, occurrence and transformation in nature, effects and dose-response relationships in humans, kinetics and metabolism, effects and dose-response relationships in animals. Each of these sessions is summarized below followed by recommendations for areas of future research.

Methods and Problems of Analysis

Summary

There are a number of sensitive physical and chemical techniques for analysis of cadmium. Al-

though these methods may be currently applied to a variety of environmental and biological matrices, careful sample preparation and analytical calibration are essential to assuring precision and reliability for different sample types.

Recommendations for Future Research

There is a need for practical methodologies for cadmium speciation (chemical form and complexation) in environmental samples and standard reference materials for environmental and biological samples. Interlaboratory calibration studies should be made for sample types of concern to both the environmental and human health effects of cadmium. Data from these calibration studies should be included whenever possible in published reports where cadmium analyses have been performed.

Release of Cadmium into the Environment

Summary

In the past, emission of cadmium into the environment has occurred primarily as the result of industrial processes. Over the past decade, models have been developed for assessing the environmental flow of cadmium and efforts made to reduce emissions in some localities. A recently developed stochastic/statistical model for estimating dietary intake of cadmium as the result of sludge utilization on crops was presented at the conference and discussed in relation to current concerns about this problem area.

Recommendations for Future Research

There is a need to further understand the magnitude and rates of cadmium flow through both

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specific areas surrounding emission sources and the general environment. The effects of climatic variations on mobilization of deposited cadmium also need further study.

Occurrence and Mobility in Nature: Terrestrial and Aquatic Ecosystems

Summary

The bioavailability of cadmium to edible plants from soils treated with sewage sludge was reported to be affected by a number of factors including plant species involved, soil pH, presence of other trace elements, and rate of sludge application. Studies with livestock fed corn grown on sludge-treated soils disclosed increased renal and hepatic concentrations of cadmium in these animals. Movement of cadmium through estuarine ecosystems and uptake by commercially important benthic shellfish was found to be influenced by a number of variables of which salinity appears to be of primary importance. The toxic potential of cadmium to one species (the American oyster) was reported to be largely dependent upon a low molecular weight cadmium-binding protein.

Recommendations for Future Research

Further studies are needed to identify other factors such as speciation of cadmium in soils which influence the rate and magnitude of cadmium uptake by edible plants grown in different types of soil. Additional research is also needed to examine those factors which influence the relationship between movement of cadmium through aquatic ecosystems and uptake, and the toxicity of cadmium to commercially important biological species.

Kinetics and Metabolism

Summary

Data on factors influencing the kinetics and toxicity of cadmium were presented demonstrating a markedly higher absorption from the gut after oral exposure in suckling animals as compared to adults. Dietary exposure to fly ash did not influence the absorption or toxicity of cadmium. Cadmium absorption and/or retention was shown to be influenced in Japanese quail by the dietary intake of zinc, iron (III), and ascorbic acid. Another aspect of interactions between cadmium and essential nutrients concerns the influence of cadmium on zinc,

copper, and iron metabolism. Particular emphasis was given to the effects of oral cadmium exposure on the lungs of animals of varying zinc status and the effects of similar cadmium-zinc combinations on fetal development. Effects on the fetus were further associated with changes in fetal iron and copper metabolism. Tissue levels of cadmium in rats were also shown to be altered by concomitant selenium exposure. However, in other studies no difference in cadmium binding to various cellular proteins was observed in relation to treatment with selenium.

Studies on humans and animals regarding the biliary excretion of cadmium indicated considerably lower values than previously reported. Biliary excretion of cadmium, however, could represent a large excretion route in comparison with urinary elimination. The possibility of an enterohepatic circulation of cadmium could not be ruled out, although fecal elimination in rats was shown to be greater than biliary excretion.

Another observation of potentially great importance concerned the high renal uptake of cadmium after oral administration of cadmium—metallothionein. The synthesis and degradation of metallothionein in various tissues after exposure to cadmium or zinc was discussed in relation to its involvement in general cadmium metabolism, and a role for a calcium binding protein in intestinal uptake of cadmium was proposed. A model for cadmium metabolism in man was presented with calculations for cadmium accumulation in eight body compartments. Some of the assumptions made in the modeling procedure have been confirmed by recent data but additional empirical data are needed to confirm the assumptions. The model also requires additional empirical data on a number of variables such as the accumulation of cadmium in blood after defined exposures, as well as information on inter-individual variation in cadmium metabolism, particularly in relation to nutritional factors.

Recommendations for Future Research

Future research is urgently needed to assess the effects of cadmium on reproduction in female workers and the possibility that young organisms may be particularly susceptible to cadmium uptake and toxicity in comparison with adults.

Future studies are needed to determine if an enterohepatic circulation for cadmium exists in humans.

The altered pharmacokinetics of cadmium following ingestion of metallothionein indicate the need for evaluation of this phenomenon in relation to renal accumulation of cadmium in humans after consumption of various foodstuffs derived from

animal viscera.

There is a need for further long-term studies investigating the importance of interactions between cadmium and essential elements and their possible role in altering tissue responses to cadmium.

There is a need to obtain human genetic data whenever possible and measure inter-individual variations in absorption, retention, and inhalation parameters of cadmium metabolism in humans.

A model for cadmium metabolism in humans should be developed which corresponds to an occupational exposure format, with intervals of high and low exposure to cadmium via food and air.

Effects and Dose-Response Relationships in Humans

Summary

Renal effects induced by cadmium exposure in industry as well as from general environmental exposure in Japan were discussed in a number of papers. Both renal glomerular and tubular effects were reported among cadmium workers in Belgium, and tubular effects among exposed Japanese were also discussed. It was noted that personal hygiene habits are of major importance in occupational exposures for calculating actual exposures and resulting effects. The measurement of β_2 -microglobulin and other low molecular weight proteins in urine was used by several investigators as an index of cadmium toxicity. This parameter seemed to be generally accepted as a means for evaluating renal tubular dysfunction. The significance of moderate increases in the urinary excretion of β_2 -microglobulin in plasma observed to occur early in the course of cadmium exposure (either as a reflection of a decreased glomerular filtration or as a result of increased synthesis of β_2 -microglobulin) indicate the need for more careful interpretation of urinary findings at early stages since enhanced excretion of this protein may reflect an increase in circulating levels. One investigation on cadmium-exposed workers and one study on the general population in Japan demonstrated the existence of a relationship between cadmium levels in urine and the prevalence of glomerular and tubular dysfunction. The data from Japan also showed that increased excretion of low molecular weight proteins in urine and renal tubular dysfunctions appeared more frequently in most of the polluted areas than in the control areas, although the dose-response relationship between these findings and degree of cadmium pollution was

not necessarily explicit. Several papers demonstrated that an excess prevalence of β_2 -microglobulinuria was associated with cadmium exposures both in cadmium industries and in population groups exposed to cadmium in the general environment in Japan. Similarities were also noted between the osteomalacia reported in a few cadmium workers with tubular dysfunction from the United Kingdom and the Itai-Itai disease found in a cadmium-polluted area of Japan. Another issue which attracted considerable attention concerned the possibility of a carcinogenic effect of cadmium in man. Data presented at the conference included preliminary analysis of cancer mortality among Swedish workers in a nickel-cadmium battery factory and cadmium-copper alloy plant. Although no increase in general cancer occurrence was reported, it was noted that there was a trend towards an increased mortality and incidence of prostatic cancer; this increase, however, was not statistically significant. It was not possible from the evidence presented, to draw a firm conclusion regarding the carcinogenicity of cadmium in humans.

Recommendations for Future Research

There is a need for further studies, preferably internationally coordinated, concerning the occurrence of cancer among cadmium-exposed workers as well as additional evaluations of population groups exposed to cadmium from the general environment.

It is recommended that future epidemiological studies of cadmium exposed persons include β_2 -microglobulin determinations for both plasma and urine as well as parameters of glomerular function.

Based on the relationship between proteinuria and age, there is a need for age-matched control groups in future epidemiological studies.

Careful follow-up studies on population groups with renal (glomerular and tubular) dysfunction due to cadmium are needed to determine the extent to which these population groups exhibit different morbidity or mortality patterns.

Both epidemiological and clinical studies on the relationship between β_2 -microglobulinuria and renal tubular dysfunctions are needed and the mechanism of β_2 -microglobulin increase in plasma should be more carefully studied in order to determine whether the increase is the result of the increased production in plasma or is due to glomerular damage.

There is a need to study the occurrence of hypertension in human populations exposed to cadmium from the general environment.

Effects and Dose-Response Relationships in Animals

Summary

Studies reported in this session were focused on both the doses of and types of effects known to be produced by cadmium in experimental animal systems. A chronic cadmium exposure experiment in monkeys was related to renal concentrations of cadmium which produced histopathological changes. These findings were related to the onset of renal tubular dysfunction. A survey study of horses also related renal concentrations of cadmium to histopathological changes in kidneys of the same animals. The teratogenic effects of cadmium in rats following acute administration were discussed in relation to antagonistic effects of cadmium on placental zinc transport and metabolism. The generation of cadmium-induced hypertension in rats was related to the presence of antagonistic or synergistic trace elements, genetic susceptibility, and dietary salt content. The important relationship of cadmium metallothionein to the hepatic and renal metabolism of cadmium was assessed by a variety of techniques. Circulating cadmium metallothionein was detected in the plasma of cadmium treated animals before the development of tubular damage. The role of metallothionein in protecting against the chronic but not acute inhibitory effects of cadmium on hepatic drug metabolism was observed in male but not female rats. Cadmium interactions with liver nuclei were evaluated in relation to induction of cadmium metallothionein synthesis. The mechanism of cir-

culating cadmium metallothionein uptake and toxicity to the kidneys was evaluated by several authors using both biochemical and combined ultrastructural/biochemical techniques. While the question of the exact mechanism of cadmium metallothionein toxicity remains to be resolved, the early uptake of cadmium metallothionein by renal lysosomes was demonstrated using both biochemical and x-ray microanalytical techniques.

Recommendations for Future Research

Further chronic low-level cadmium exposure studies in animals are needed to assess the toxic effects of this agent. Generation of realistic animal to human extrapolation models would greatly aid the interpretation of animal data for human health risk assessment.

More studies dealing with cellular mechanisms of cadmium toxicity and the relationship of cadmium metallothionein to toxic manifestations are also needed.

Further evaluation of interactive factors such as dietary composition which influence the toxicity of cadmium at chronic low-level exposures are needed for interpretation of animal and human health risk assessment.

Further studies are needed for the development of agents which will bind cadmium *in vivo* and permit its more rapid elimination from the body.

Chronic low-level cadmium exposure studies are needed to investigate biochemical and physiological mechanisms involved in the induction and maintenance of hypertension in rats.